PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TX/4-32732A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/001323	International filing date *(day/month/year)* 12.02.2004	Priority date *(day/month/year)* 13.02.2003
International Patent Classification (IPC) or national classification and IPC C07D401/14, C07D403/14, A61K31/44, A61K31/40		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.07.2004	07.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Guspanova, J Telephone No. +49 89 2399-7834

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/001323

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-24 as originally filed

   Claims, Numbers

   1-10 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/001323

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1(part)-10(part) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1(part)-10(part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1(part)-10(part)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1(part)-10(part)
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Re Item III.

For the assessment of the present claim 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV.

The following separate inventions have been found in the present application:

1. Compound of formula I wherein R is radical of formula (a) given in claim 1
2. Compound of formula I wherein R is radical of formula (b) given in claim 1

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:
A special technical feature which links both inventions mentioned above can be seen in a structural feature which is indolylmaleimide moiety substituted by an additional heterocyclic substituent (pyrid-2-yl or indol-4-yl). However, such a structural feature is known in the state of the art. See example 87 in D1.
A special technical feature which links both inventions mentioned above can also be seen in the use of compounds for treatment of disorders or diseases mediated by protein kinase C. However, such a use is ascribed for the compound of the example 87 in D1.

In respect to what is stated above, there is nothing in common which would link the two mentioned inventions together and the requirement for unity referred to in Rule 13.1 PCT is therefore not fulfilled.

The application will be prosecuted on the basis of the invention first mentioned in the claims.

Re Item V.

1. **Relevant prior art**

D1: US-A-5 057 614 (DAVIS PETER D ET AL) 15 October 1991 (1991-10-15)
D2: WO 02/38561 A (NOVARTIS ERFIND VERWALT GMBH ; ALBERT RAINER (CH); NOVARTIS AG (CH); C) 16 May 2002 (2002-05-16)

2. **Novelty**

The present application relates to the compounds of general formula I wherein R is radical of formula (a), substituted pyrid-2-yl radical (claim 1), to a process for the preparation thereof (claim 6) and to the use of these compounds for the treatment of disorders mediated by T lymphocytes and/or PKC or GSK-3β (claims 7-9).

D1 discloses compounds of general formula I (claim 1) which compounds are inhibitors of protein kinase C (PKC; column 11, lines 38-41). The most part of these compounds differ from those of the present application (formula I wherein R means (a)) in the nature of a cyclic substituent attached to the indolylmaleimide moiety. Only three compounds of the Examples 86 and 87 wear a pyridyl radical at the said position. However, they are not substituted by further substituents.

D2 discloses compounds of general formula I which compounds are inhibitors of PKC (page 36, paragraph 1). They differ from those of the present application (formula I wherein R means (a)) in the nature of a cyclic substituent attached to the indolylmaleimide moiety. Pyridyl group is not disclosed as a substituent for indolylmaleimide basic structure.

Since certain differences have been found between the compounds presently claimed and the compounds of the prior art, the part of the subject-matter claimed in the first invention is regarded novel, according to Article 33(2) PCT.

3. **Inventive step**

The problem underlying the present invention is seen in the provision of further indolylmaleimide derivatives useful for the treatment of disorders or diseases mediated by T lymphocytes and/or PKC or GSK-3β.

The closest prior art represented by document D1 discloses a broad family of compounds which differ from those of the present application (formula I wherein R means (a)) in a character of a cyclic moiety attached to the indolylmaleimide basic core as already discussed under Novelty. Solely three compounds of the Examples 86 and 87 wear a pyridyl group at the said basic core and only one of them is pyrid-2-yl group. The others two are pyrid-3-yl and pyrid-4-yl. However, none of these three compounds is substituted by a further substituent.

The solution to the problem stated above resides in the provision of the compounds of formula I wherein R is substituted pyrid-2-yl group. Pharmaceutical data for the compounds claimed are given on pages 16-20. The technical problem underlying the present application has been solved. Starting with the D1 compounds the skilled person must have chosen one certain compound (Example 87) from the large number of D1 compounds and further introduce at least one substituent to the position 6 of pyrid-2-yl group. Compounds of Examples 86 and 87 having a pyridyl group on indolylmaleimide basic core are not specified as preferred embodiments in the specification of D1. According to the dependent claims of D1 phenyl group as well as 3-indolyl group are considered as the preferred embodiments. Other cyclic moieties are also exemplified in the description of D1. Only one example is given for pyrid-2-yl group. Having regard to what was stated above, the solution to the stated technical problem proposed in the independent claim 1 (compounds of formula I wherein R is pyrid-2yl) is considered non-obvious. Document D2 does neither explicitly disclose nor suggest a pyrid-2-yl group as a substituent of indolylmaleimide.

Therefore, an inventive step of the first invention mentioned above is acknowledged, according to Article 33(3) PCT.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 03/076398	18.09.2003	05.03.2003	08.03.2002

This document is not taken into consideration for the examination at present.